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EXAMINER	
CELSA, P	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/06/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

file copy

Office Action Summary

Application No.	Applicant(s)
08/796,164	Stamler et al.
Examiner	**Group Art Unit**
Bennett Celsa	1654

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-62* is/are pending in the application.

Of the above, claim(s) *1-9, 23, 33-39, and 47-62* is/are withdrawn from consideration.

☒ Claim(s) *43 and 44* is/are allowed.

☒ Claim(s) *10-22, 24-32, 40-42, 45, and 46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *, 8, 10 -1*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-62 are currently pending.

Claims 10-22, 24-32 and 40-46 are under consideration.

Claims 1-9, 23, 33-39 and 47-62 are withdrawn from further consideration as being drawn to a non-elected invention.

Election/Restriction

1. Applicant's election with traverse of Group IV (claims 10-22, 24-32 and 40-46) in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the Group VI invention (claims 35-39) should be grouped with the elected group since polynitrosated hemoglobins are generic to elected subject matter directed to SNO-hemoglobins . This is not found persuasive for the reasons recited in the restriction (e.g. chemical structure distinctness/different propeties/different methods of making/use) e.g. because the Group VI invention is directed to patentably distinct methods from those of Group IV and result in compositions of different structure and scope which necessitate different searches from those of the elected invention..

The requirement is still deemed proper and is therefore made FINAL.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 40-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating NO mediated diseases or disorders using NO donating compounds, the specification does not reasonably provide enablement for preventing diseases or disorders mediated by NO. The specification fails to provide evidence regarding the correlation between treating diseases/dirorders with NO donating compounds and the *prevention* of any disease state or disorder including those listed on pages 1-4 of the specification. For claims drawn to pharmaceuticals and methods of treatment generally require supporting data because of the unpredictability in biological responses to therapeutic treatments. Further, the burden of enabling the prevention of a disease (ie. the need for additional testing) would be greater due to the need of screening those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. For, the efficacy of a drug treatment in vivo faces unfavorable obstacles not present in vitro models. As such, in vivo utility necessarily involves unpredictability with respect to physiological activity of an asserted process in humans. See discussion in Ex parte Kranz, 19 USPQ2d 1216,1218-1219 (6/90). For example, drug delivery to the targeted area must survive the acidic environment of the stomach if administered orally. Additionally, the delivery of the drug across necessary cell surfaces in amounts needed to be efficacious, but not lethal to the

organism, necessitates sensitive testing in order to adequately determine the proper human dosage. Accordingly, for the reasons recited above, the specification fails to enable prevention using the scope of compounds for the disease states encompassed by the presently claimed invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 12, 15-22, 24-32, 40, 41, 42 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "low" in claims 12, 15, 16 and18 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. .

B. In claim 16, the phrase "selected for the oxidation state of the heme iron and for the oxygen state" is indefinite as to the means and criteria for selection, improper antecedent basis for "the oxygen state" and confusion as to what oxidation state the phrase "the oxygen state" is referring to e.g. the heme iron or some other compound(s) oxidation state.

C. Method claims 16-22, 24-32 and 40-41are indefinite as to the mode of administration and the administrative amounts.

D. In claims 21 and 22, "a form of SNO-Hb" is indefinite as to what form of Hb is encompassed within the metes and bounds of this claim.

E. In claim 40 the phrases "a disease or medical disorder which can be ameliorated ... affected by the disease or medical disorder" and the term "nitrosyl-heme-containing donors of NO" are indefinite as to the diseases, disorders and NO donors that are within the metes and bounds of the claims.

F. In claims 42 and 45, the NO:heme ratio appears to be contradictory: "less than 1:100" OR "greater than about 0.75".

Double Patenting

6. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 10-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 9-15 of copending Application No. 08/616,371. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 17-32 and 40-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-21 and 23-29 of copending Application No. 08/616,371. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is overlap with respect to the nitrated hemoglobins claimed for use in the same or similar methods..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 10-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44-50 of copending Application No. 08/667,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods contain the same steps, reactants and final products and the compositions differ only with respect to scope..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 42 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Moore et al., J. Biol. Chem. Vol. 251, No. 9 (5/76) pages 2788-2794. Moore et al. disclose a "stock nitrosylhemoglobin solution" which comprises nitrosyl-deoxyhemoglobin in a buffer and which contains an NO:heme ratio within the scope of the presently claimed invention (e.g. greater than

about 0.75) which is formed by reacting aqueous deoxyhemoglobin, buffer and NO solution. (E.g. see page 2789, left column under "Materials and Methods").

14. Claims 42, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. and Kharitonov et al., Methods in Nitric Oxide Research (Wiley & Sons Ltd:1996)

Moore et al. disclose a "stock nitrosylhemoglobin solution" which comprises nitrosyl-deoxyhemoglobin in a buffer and which contains an NO:heme ratio within the scope of the presently claimed invention (e.g. greater than about 0.75) which is formed by reacting aqueous deoxyhemoglobin, buffer and NO solution. (E.g. see page 2789, left column under "Materials and Methods"). The Moore reference method differs from the invention of claim 46 by Moore's use of deoxyhemoglobin instead of oxyhemoglobin as presently claimed. However, Kharitonov et al. disclose that nitrosylated hemoglobins can be formed by nitrosylation of either deoxyhemoglobin or oxyhemoglobin as the starting reactant by merely optimizing the concentration of added NO (e.g. see pages 42-43) relative to hemoglobin. Optimization of NO to oxy/deoxy -hemoglobin starting concentration to achieve nitrosylated hemoglobin is within the skill of the art. Accordingly, it would have been prima facie obvious to the skilled artisan to react NO with either deoxy/oxy -hemoglobin in an amount within the scope of the presently claimed invention to achieve the desired nitrosylated hemoglobin since both the Moore and Kharitonov references

disclose nitrosylated hemoglobins and Kharitonov discloses the interchangeability of the starting products (e.g. oxy or deoxy -hemoglobin).

15. Claims 10-22, 25-28, 30-32 and 40-41 under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Stamler et al. discloses the therapeutic use of "low molecular weight" thiols, S-nitroso-protein and amino acid compounds (e.g. S-nitroso-hemoglobin or myoglobin) for regulating protein function, inhibiting platelet function, cellular metabolism including effecting vasodilation; increasing blood oxygen transport by hemoglobin and myoglobin; NO delivery; *in vitro* nitrosylation of molecules present in the body (e.g. see Abstract; pages 1-3 and claims). Thus, the disclosed compounds are deemed useful in treating cardiovascular disorders, brain disorders and respiratory disorders within the scope of the presently claimed invention. Stamler discloses a thionitrosylated hemoglobin composition (e.g. see page 58 and claims 13-16) comprising reacting hemoglobin in the presence of oxygen with a nitrosating agent (e.g. SNOAc). Stamler teaches the use of equimolar amounts of nitrosating agent and Hb. Optimizing nitrosylating amounts to achieve "excess" nitrosation of hemoglobin to insure nitrosylation of hemoglobin would be obvious to the skilled artisan at the time of applicant's invention. The reference method of forming thionitrosylated oxygenated hemoglobin would render obvious the formation of thionitrosylate deoxygenated hemoglobin under anaerobic conditions as presently claimed. The reference specifically discloses the use of nitrosylated proteins (e.g. S-nitroso hemoglobin) and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations

thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims). The combination of nitrosating agents (e.g. thionitrosylated "Low" molecular weight and "high" molecular weight compounds; e.g. nitrosothiol, glutathione and hemoglobin) would be prima facie obvious to the skilled artisan at the time of applicant's invention in order obtain the increased pharmaceutical effects of the agents.

16. Claims 10-22, 24-32 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier) and Klatz et al., U.S. Pat. No. 5,395,314 (3/95: file 6/93 or earlier).

The discussion of the teaching of the Stamler et al. reference in the above rejection under 35 USC103 is hereby incorporated by reference in its entirety. To summarize, the Stamler et al .reference discloses the use of S-nitrosating agents (e.g. low molecular weight e.g. glutathione and hemoglobin derivatives) to treat disorders by achieving a variety of physiological effects including vasodilation; radical scavenging ; NO and oxygen delivery. The above Stamler reference does not explicitly disclose the use of nitrosating agent(s) to act as a blood substitute or treat sickle cell anemia. Feola et al. disclose the use of "blood substitutes" to restore blood volume, transport oxygen and reduce vasoconstriction (e.g. vasodilate) by the use of hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7). Klatz et al. disclose a brain

resuscitation and organ preservation composition which comprises perfluorocarbons which act as "a blood substitute" which "transport(s) oxygen in a manner similar to hemoglobin" (e.g. see Abstract, col. 1, col. 4, lines 1-25). The Stamler et al. reference provides the skilled artisan with motivation to use nitrosating agents alone or combined to treat disorders of diseases to which vasodilation and oxygen/NO transport would prove to be therapeutic. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize thionitrosating agents (e.g. hemoglobin, glutathione) as blood substitutes to treat blood disorders such as sickle cell anemia since the Feola reference discloses the use of hemoglobin and thiol containing blood substitutes to treat anoxic blood disorders (e.g. sickle cell anemia as disclosed by Feola) and Stamler provides a reasonable expectation that nitrosating agents will be successful to achieve the desired effects of blood substitutes. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize nitrosating agents for organ preservation since the Katz reference provides motivation to utilize compositions such as perfluorocarbons for their ability to act as "blood substitutes" and hemoglobin oxygen transporters and Stamler teaches that nitrosating agents would be successful to achieve the desired effects of blood substitutes and also act as effective hemoglobin oxygen transporters.

17. Claims 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler, U.S. Pat. No. 5,583,101 (12/96: filed 7/94). Stamler discloses a method of inhibiting or relaxing skeletal muscle contraction and disease states resulting therefrom by administering nitric oxide containing compounds (e.g. see Abstract and Patent claims). Stamler clearly includes the use of

nitrosylated heme containing proteins including hemoglobin and serum albumin (e.g. see col. 2, lines 7-25). Accordingly, the use of a nitrosylated heme containing protein to treat a disease or disorder within the scope of the presently claimed invention would have been obvious to the skilled artisan in view of the Stamler reference since the skilled artisan would have been motivated to select a nitrosylated heme protein for use in the Stamler method.

Allowable Subject Matter

18. Claims 43 and 44 are allowable over the prior art of record.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (AU 1654)

BC

July 1, 1998